



**Stern countenance.** Tim McCaughan says his condition leads people to take him more seriously than he intends.

## NEUROLOGICAL DISORDERS

# The Mystery of the Missing Smile

Genetic studies and an ineffective abortion drug have provided some of the few clues researchers have about a rare disorder that hampers facial expressions

**BETHESDA, MARYLAND**—People can't always tell when Tim McCaughan is joking. Several years ago, a recently hired colleague congratulated him on a promotion, saying she was sure it was well-deserved. "Well, how would you know?" McCaughan quipped, playfully suggesting that maybe he didn't deserve the promotion after all. But his face didn't convey that he was joking, and the woman thought he was being a jerk. McCaughan has a rare neurological condition called Möbius syndrome that limits his ability to smile and make other facial expressions.

"People often take me much more seriously than I really am," says McCaughan, a senior producer at CNN who oversees the news network's coverage of the White House. He eventually managed to smooth things over with his colleague, who became his wife a few years later. "I'm still living that one down," he says.

McCaughan's case of Möbius syndrome is on the milder side of a wide spectrum. Many people have more extensive facial paralysis that impairs their speech and causes difficulties with eating. Limb deformities such as clubfoot often accompany Möbius syndrome. And for some unknown reason, autism appears to be far more common in people with the syndrome than in the general population.

An international group of neurologists, geneticists, and other specialists gathered here recently for the first scientific conference\* on this mysterious congenital disorder. They explored possible genetic and environmental triggers, discussed potential treatments, brainstormed research strategies, and hashed out a consensus set of diagnostic criteria. "This is really at such an early stage," says John Porter, a program director at the National Institute of Neurological Disorders and Stroke, one of the meeting's sponsors. The meeting was a good start, but cracking the biology of Möbius syndrome isn't going to be easy, Porter says. "I think the mechanistic insights are going to take a while."

### Frozen faces

The syndrome is named for Paul Julius Möbius, a German neurologist who published an early description of it in 1888. (He was also the grandson of August Ferdinand Möbius, the mathematician of Möbius strip fame.) According to a statement developed at the conference, the syndrome's defining characteristics are facial weakness and impaired ability to move the eyes to the side—symptoms

\* Moebius Syndrome Foundation research conference, 24–25 April 2007.

that are present at birth and don't worsen with age. Researchers estimate that Möbius syndrome occurs in 1 of every 50,000 live births, affecting boys and girls equally often.

The core symptoms of Möbius syndrome point to defects in two cranial nerves: the abducens nerve, which innervates the lateral rectus muscles that rotate the eyes toward the side of the head; and the facial nerve, which innervates the muscles of the face. Yet, there doesn't seem to be a single neuropathological signature of the disorder.

At the conference, George Padberg, a neurologist at the University Medical Center in Nijmegen, the Netherlands, described magnetic resonance imaging studies he and colleagues have done to visualize the nervous system in people with Möbius syndrome, as well as findings from electrophysiological tests of nerve function. This work has revealed a variety of defects. In some patients, the cranial nerves appear to be damaged or even missing. Others have abnormalities in the brainstem that include—and often extend beyond—the region where the abducens and facial nerves originate. Based on these and other findings, Padberg suspects that Möbius syndrome results from genetic miscues that derail the embryonic development of the brainstem.

But the search for the relevant genes has yielded little fruit so far. The rarity of the disorder, coupled with the fact that only about 2% of cases are inherited, makes it difficult to find a sufficient number of subjects for genetic linkage studies, says Ethylin Wang Jabs, a geneticist at Johns Hopkins University in Baltimore, Maryland. The complexity of the disorder and lack of precise diagnostic criteria have also complicated matters, Jabs says. Padberg's group, for example, has published studies identifying regions of chromosome 3 and chromosome 10 as likely loci of genes related to inherited Möbius syndrome in two Dutch families, but other researchers point out that individuals in these families lack the eye-movement irregularities necessary to qualify as true cases of Möbius syndrome. (Padberg now agrees.)

Now that there's a more precise definition of the disorder, the next step for finding Möbius genes, Jabs and others say, will be to create a central database in which researchers can share clinical and genetic data on Möbius patients. Jabs has started a database that now includes clinical data and/or DNA samples from 89 people with Möbius syndrome and more than 100 relatives, and other research teams have similar data.

Researchers are also looking to related disorders and mouse models of brain develop-

ment for clues. At the conference, Elizabeth Engle, a pediatric neurologist at Children's Hospital Boston, described her team's research on several inherited neurological conditions that share symptoms with Möbius syndrome. Athabaskan brainstem dysgenesis syndrome (ABDS), named for the Native American population in which it was first described in 2003, causes impaired lateral eye movements and sometimes facial weakness as well. Similar symptoms had been reported in mice lacking a gene called *Hoxa1*, one of a family of genes that guide embryonic development. People with ABDS inherit a truncated copy of the human version of the gene, *HOXA1*, Engle and colleagues reported in 2005 in *Nature Genetics*. It's possible that spontaneous mutations in *HOXA1* could be involved in Möbius syndrome, Engle says, but so far no one has looked. Jabs has been screening her Möbius patients for mutations in two other *Hox* genes, *HOXB1* and *HOXB2*, based on findings of facial nerve abnormalities in mice lacking these genes. So far, however, nothing has turned up.

Misoprostol is typically used in the first trimester of pregnancy, and in the sample of Möbius children Ventura has worked with, misoprostol exposure occurred on average about 40 days after conception.

Some researchers have proposed that Möbius syndrome can result from a transient interruption in fetal blood circulation, and Ventura and others think the misoprostol findings fit with that idea. One possibility is that uterine contractions evoked by the drug disrupt fetal blood supply during a crucial stage of development, causing neural circuits in the brainstem to be permanently miswired.

Other researchers are exploring the apparent link between Möbius syndrome and autism. Research teams from Sweden, Canada, and Brazil reported at the conference that roughly a third of their Möbius patients have autism spectrum disorders; teams from the United States and the Netherlands reported autism rates of 5% or less, however. One possibility is that the miswiring of the brainstem that occurs in Möbius syndrome somehow predisposes

long-term effects of such relative social deprivation could be substantial, Schmidt says.

Unfortunately, there's little help for the neurological symptoms of Möbius syndrome. One dramatic exception is "smile surgery" developed by plastic surgeon Ronald Zuker at the Hospital for Sick Children in Toronto, Canada. At the conference, Zuker described the 8-hour procedure, which he has performed in hundreds of children since the late 1980s. Zuker's team transplants a small piece of muscle from the patient's thigh to the face and positions it so that it will raise the upper lip when it contracts. To innervate the transplanted muscle, the surgeons usually reroute a nerve that innervates the masseter, the muscle that raises the lower jaw during chewing. Initially, the patients need to think about clamping their jaws to fire the nerve and elicit a smile, Zuker says, but with time the smile becomes more automatic.

Zuker showed several before-and-after videos that revealed striking differences. One boy, when asked to smile prior to surgery,



**Something to smile about.** Möbius syndrome robbed Chelsey Thomas of a smile (left); plastic surgeons gave her a new one in two stages.

### A troubling drug problem

Garbled genes aren't the only way to get Möbius syndrome. Since the mid-1990s, dozens of cases of Möbius syndrome have been linked to misoprostol, a drug commonly used by women in Brazil to induce abortion. Elective abortion is illegal in Brazil, but misoprostol is cheap and widely available, says pediatric ophthalmologist Liana Ventura of Fundação Altino Ventura, a medical charity in Recife, Brazil. Although misoprostol is used in three-quarters of abortion attempts in Brazil, it is not particularly effective: Up to 80% of pregnancies continue to term, and about 20% of those result in an infant with Möbius syndrome, Ventura says.

people to autism. Another, more speculative hypothesis is that the limited facial expressions in infants with Möbius syndrome hinder social interactions early in life, thereby stunting the development of the brain's social circuitry and leading to social impairments characteristic of autism.

"We have evolved to use our faces as a primary means of communication, both through speech and facial expressions," says Karen Schmidt, a biological anthropologist at the University of Pittsburgh in Pennsylvania who studies facial behavior. An infant with Möbius syndrome is less able to smile and interact with others, and many children with Möbius syndrome are shunned by their peers. The

could only muster an expression that looked closer to a grimace or frown, the corners of his mouth moving slightly sideways and downward. After surgeries on both sides, his smile was unmistakable, and he even seemed to modulate it according to whether he actually felt like smiling or was merely indulging the cameraman for the umpteenth time.

Still, smiles aren't for everyone—at least not all the time. McCaughan, whose work at CNN has given him the opportunity to travel with and interview several U.S. presidents over the years, says his condition sometimes works in his favor. "I'd say I've got the best deadpan in the business when asking a question."

—GREG MILLER

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